Challenge TB - Core project on TB prevention

Year 2

Annual Report

October 1, 2015 – September 30, 2016

Submission date: November 16, 2016

Cover photo: *Cover photo: Portrays the signing of the sub-award agreement (source: http://theipstone.com)*

This report was made possible through the support for Challenge TB provided by the United States Agency for International Development (USAID), under the terms of cooperative agreement number AID-OAA-A-14-00029.

Disclaimer
The authors' views expressed in this publication do not necessarily reflect the views of the United States Agency for International Development or the United States Government.

Contents

List of Abbreviations and Acronyms

3HP	3-month regimen of weekly isoniazid and rifapentine therapy
6H	6-month regimen of daily isoniazid therapy
DSMB	Data Safety Monitoring Board
HIV	human immunodeficiency virus
INH	isoniazid
IPT	isoniazid preventive therapy
LSHTM	London School of Hygiene and Tropical Medicine
LTBI	latent tuberculosis infection
MCC	(South African) Medicines Control Council
p3HP	periodic 3-month regimen of weekly isoniazid and rifapentine therapy
QFT	QuantiFERON
RIF	rifampicin
RPT	rifapentine
TB	Tuberculosis
TSC	Trial Steering Committee
TST	tuberculin skin test
WHO	World Health Organization

1. Executive Summary

The World Health Organization (WHO) recommends at least six months of isoniazid (6H) for persons living with HIV. However, 6H remains poorly implemented in most high burden TB countries. In its 2015 guidelines, WHO includes 3HP as a latent tuberculosis infection (LTBI) treatment option for high-income and upper middle-income countries with TB incidence rates <100/100,000. One trial comparing 3HP to 6H in a high burden country suggests that a single round of 3HP has less toxicity, better treatment completion rates, and similar efficacy in preventing TB. In high burden settings, 6H and 3HP provide protection of limited duration probably due to high ongoing transmission and reinfection. Continuous isoniazid preventive therapy has been shown to provide more durable protection in high burden settings, but is not currently policy outside of a handful of countries, and the actual uptake is poor. Giving 3HP periodically may provide durable protection, be easier for health systems to implement, and may be associated with better adherence and fewer side effects.

The project has two objectives:

1) to compare treatment completion of a single round of 3HP to 6H
2) to compare effectiveness of a single round of 3HP to two annual rounds of 3HP.

The purpose of comparing a single round of 3HP to 6H is to demonstrate the feasibility of implementing 3HP in high burden countries. The purpose of comparing a single round of 3HP to pulsed 3HP is to assess whether in high-incidence settings an annual round of 3HP has superior effectiveness for preventing incident TB over a single round of 3HP. Both are meant to generate evidence to guide a WHO recommendation for the use of 3HP in high-incidence settings.

The trial is named WHIP$_3$TB (Weekly High dose Isoniazid and Rifapentine (P) Periodic Prophylaxis for TB).

For this study a total sample size of 4000 participants (400 in the 6H arm: 1800 in the 3HP arm: 1800 in the pulsed 3HP arm) will be adequate to meet the primary objective on the comparison of TB incidence in the 3HP versus the pulsed 3HP arm, with a superiority design assuming 80% power, effectiveness (i.e. reduction of cumulative TB incidence) of 40%, two years of follow up and 20% loss to follow up.

KNCV Tuberculosis Foundation, the prime recipient of Challenge TB, is the leading CTB partner in this project. KNCV has delegated daily management related to the conduct of the trial to the sub-recipient the Aurum Institute (Aurum), while KNCV will be responsible for the overall project, including monitoring and evaluation. Activities for trial responsibilities are delegated to Aurum. Aurum is subcontracting several activities[1]:

- trial implementation to local research partners:
    - Mozambique: Instituto Nacional de Saúde – Mozambique
    - Ethiopia: College of Health Sciences, Addis Ababa University
    - South Africa: Perinatal HIV Research Unit, A Division of Wits Health Consortium (Pty) Ltd (they will enroll participants in South Africa additional to Aurum-owned sites)
- data management and adverse event monitoring to LSHTM
- data monitoring to Quintiles.

[1] These subcontracts are being finalized and will be in place (upon KNCV/PMU approval) in APA3

2. Introduction

The World Health Organization (WHO) recommends at least six months of isoniazid (6H) for persons living with HIV. However, 6H remains poorly implemented in most high burden TB countries. In its 2015 guidelines, WHO includes 3HP as a latent tuberculosis infection (LTBI) treatment option for high-income and upper middle-income countries with TB incidence rates <100/100,000. One trial comparing 3HP to 6H in a high burden country suggests that a single round of 3HP has less toxicity, better treatment completion rates, and similar efficacy in preventing TB. In high burden settings, 6H and 3HP provide protection of limited duration probably due to high ongoing transmission and reinfection. Continuous isoniazid preventive therapy has been shown to provide more durable protection in high burden settings, but is not currently policy outside of a handful of countries, and the actual uptake is poor. Giving 3HP periodically may provide durable protection, be easier for health systems to implement, and may be associated with better adherence and fewer side effects.

The trial will be conducted in South Africa, Mozambique and Ethiopia, and has two objectives:

1) to compare treatment completion of a single round of 3HP to 6H
2) to compare effectiveness of a single round of 3HP to two annual rounds of 3HP.

The purpose of comparing a single round of 3HP to 6H is to demonstrate the feasibility of implementing 3HP in high burden countries. The purpose of comparing a single round of 3HP to pulsed 3HP is to assess whether in high-incidence settings an annual round of 3HP has superior effectiveness for preventing incident TB over a single round of 3HP. Both are meant to generate evidence to guide a WHO recommendation for the use of 3HP in high-incidence settings.

The trial is named WHIP$_3$TB (Weekly High dose Isoniazid and Rifapentine (P) Periodic Prophylaxis for TB).

In Year 2 the following progress was made:

- USAID provided approval for the KNCV Tuberculosis Foundation to enter into a sub-agreement with the Aurum Institute on April 13;
- The sub-agreement between the Aurum Institute and KNCV Tuberculosis Foundation was signed by both parties;
- USAID budget approval for the period until September 30, 2016 was received;
- Establishment of Trial Steering Committee and first face-to-face meeting in December 2015
- Agreements with Sanofi and Qiagen for donation of drugs and IGRA tests were signed.
- Witwatersrand University Institutional Review Board for ethical approval as well as the Medicines Control Council (MCC) for regulatory approval (South Africa) was obtained. The protocols were submitted for approval in Ethiopia and Mozambique also, responses are awaited.
- The data safety monitoring board (DSMB) was established;
- Start of enrollment is being prepared through development of standard operating procedures (SOPs) and case report forms (CRFs); Aurum sites in South Africa have been mobilized to ensure readiness for enrollment in October 2016.
- A tender was released and responses were received from contract research organizations (CROs) for study monitoring. A CRO was selected;
- Clinical trial sites in South Africa, Mozambique, and Ethiopia as well as the CRO were selected by Aurum (through a transparent process) and Aurum is currently negotiation and developing sub-awardee agreements to be submitted to the PMU for approval in the next quarter;
- The clinical trial insurer was selected and the policy is in the process of being finalized.
- Further, a draft Gantt chart was developed indicating what has to be done (the activities) and when (the schedule), see annex 1.

In Year 2, all activities were geared towards initiating of enrollment of participants in the trial, expected to start early in Year 3 and, with follow-up for two years (Year 3, Year 4, and partly Year 5). In Year 5, the data will be analyzed and reported.

3. Progress by Objective/Sub-Objective

Objective 2. Prevention of transmission and disease progression

Sub-objective 6. Management of latent TB infection

The trial to be conducted under this core project has two objectives:

1) to compare treatment completion of a single round of 3HP to 6H
2) to compare effectiveness of a single round of 3HP to two annual rounds of 3HP.

The results of the trial are meant to generate evidence to guide a WHO recommendation for the use of 3HP in high-incidence settings.

In Year 2, all activities were geared towards initiating of enrollment of participants in the trial, expected to start early in Year 3 and, with follow-up for two years (Year 3, Year 4, and partly Year 5). In Year 5, the data will be analyzed and reported.

In Year 2 the following progress was made:

- USAID provided approval for the KNCV Tuberculosis Foundation to enter into a sub-agreement with the Aurum Institute on April 13;
- The sub-agreement between the Aurum Institute and KNCV Tuberculosis Foundation was signed by both parties;
- USAID budget approval for the period until September 30, 2016 was received;
- Establishment of Trial Steering Committee and first face-to-face meeting in December 2015
- Agreements with Sanofi and Qiagen for donation of drugs and IGRA tests were signed.
- Witwatersrand University Institutional Review Board for ethical approval as well as the Medicines Control Council (MCC) for regulatory approval (South Africa) was obtained. The protocols were submitted for approval in Ethiopia and Mozambique also, responses are awaited.
- The data safety monitoring board (DSMB) was established;
- Start of enrollment is being prepared through development of standard operating procedures (SOPs) and case report forms (CRFs); Aurum sites in South Africa have been mobilized to ensure readiness for enrollment in October 2016.
- A tender was released and responses were received from contract research organizations (CROs) for study monitoring. A CRO was selected;
- Clinical trial sites in South Africa, Mozambique, and Ethiopia as well as the CRO were selected by Aurum (through a transparent process) and Aurum is currently negotiation and developing sub-awardee agreements to be submitted to the PMU for approval in the next quarter;
- The clinical trial insurer was selected and the policy is in the process of being finalized.
- Further, a draft Gantt chart was developed indicating what has to be done (the activities) and when (the schedule), see annex 1.

Key Results

#	Outcome Indicators	Indicator Definition	Baseline: not applicable	Target Y2	Result Y2
	#/% of patients enrolled in the study	the number and percent of patients enrolled in the study during enrolment period		undefined	0
	#/% of patients completed the study	the number and percent of patients with complete primary end point data		0	0
	# of study protocol violations	the number of violations of the study protocol during the study implementation		0	0

4. Key Challenges during Implementation and Actions to Overcome Them

Challenge	Actions to overcome challenges
Technical	
Obtaining regulatory and ethical approval requires minimally half a year in each country. Submission for approval was delayed due to sub-awards with local partners not being signed yet.	Ethics and regulatory approval for Mozambique and Ethiopia have been requested before sub-awards with the local partners in both countries are signed.
Sanofi could not ship the donated drugs before ethical and regulatory approval was obtained in South Africa (received 7 September 2016).	Shipment being processed early October 2016.
Waiver needed for purchase of drugs (isoniazid and pyridoxine) needed in the trial.	Sanofi will also donate the isoniazid for the 6H arm. Aurum is exploring several ways to obtain pyridoxine as soon as possible.
Administrative	
The development/finalization/signing of the sub-agreement between the KNCV Tuberculosis Foundation and the Aurum Institute as well as the sub-awardee agreements between the Aurum Institute and their sub-awardees (LSTHM, CRO, and sites) was pending USAID sub-award approval and budget approval.	Since both approvals were in place, both KNCV and Aurum had been able to fully mobilize their teams and are making all efforts to finalize and sign the different agreements as soon as possible. The sub-agreement between KNCV and Aurum was signed. The sub-awards are in the final stages of developments.

5. Lessons Learnt/ Next Steps

Lessons learnt:

- Not applicable yet since we are still in the preparation phase of the trial

Next steps:

- Enrollment of participants will start early in Year 3 in South Africa and later in Year 3 in Ethiopia and Mozambique. We are aiming to finalize participant enrollment by end of June 2017 so that all individuals can be followed up for 24 months and the trial results will be available by the end of the CTB period. We are confident that we can finalize participant enrollment by the end of the Challenge TB (29 September 2019), which would allow for reporting on process and activities within the set reporting timelines. This would also allow for reporting on the outcomes related to objective 1 (to compare treatment completion of a single round of 3HP to 6H) while outcomes related to objective 2 (to compare effectiveness of a single round of 3HP to two annual rounds of 3HP) would be reported on after the end of the Challenge TB project period. KNCV with Aurum will develop scenarios to address potential threats and solutions related to trial planning for discussion with USAID in November 2016.

Annex 1. GANTT Chart

Gantt Prevention Project Updated Octo